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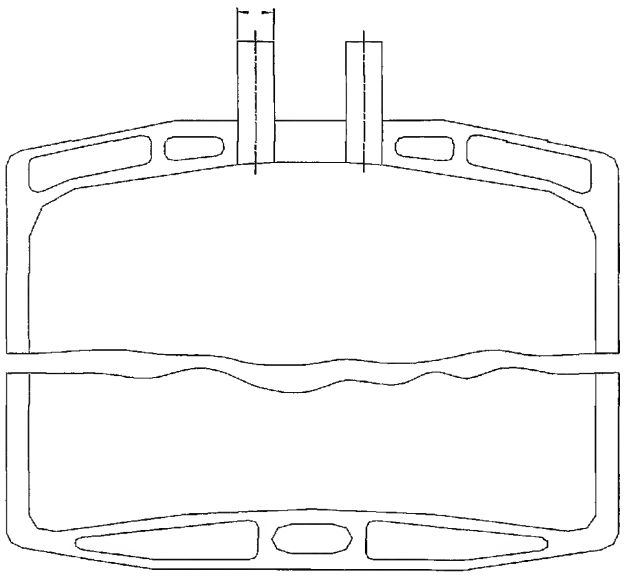
(54) Title: PROCESS FOR OBTAINMENT OF STABLE INJECTABLE ISOTONIC SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, STABLE INJECTABLE SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, PROCESS OF PACKING THE OBTAINED INJECTABLE SOLUTION IN CLOSED SYSTEM, USE OF CLOSED SYSTEM FOR PACKING GATIFLOXACIN INJECTABLE SOLUTION, USE OF OBTAINED INJ



(57) Abstract: The present invention has the premise that the use of pre-diluted preparations in closed system reduces the risk of errors in the administration of drugs, reducing the handling phases of the drug by the hospital nursing staff, in addition to reduction in contamination risks. The product obtained by the present invention is presented in the form of gatifloxacin injectable solution pre-diluted in glucose, packed in tri-laminated flexible plastic bag (closed system). Through the formulation pre-diluted in glucose and the closed system, the risks of contamination through the air or contact during the administration are prevented. The formulation is added by 5% of glucose, an isotonic solution, where diluted gatifloxacin is maintained stable when packed in tri-laminated flexible plastic bag. The gatifloxacin-based injectable solution pre-diluted in glucose, is packed in tri-laminated flexible plastic bag of closed system type and shows anti-microbial action of wide spectrum. The method of administration of gatifloxacin-based injectable solution pre-diluted in glucose shows the advantage of administering to patients gatifloxacin-based injectable solution pre-diluted in glucose, packed in tri-laminated flexible plastic bag, of closed system type, thus eliminating the ambient contact with the solution to be administered and preventing the microbial contamination by air or contact during the connection of the administration equipment, thus reducing the risks of errors in the administration of drugs, as well as the reduction of the drug handling phases by the hospital nursing staff.

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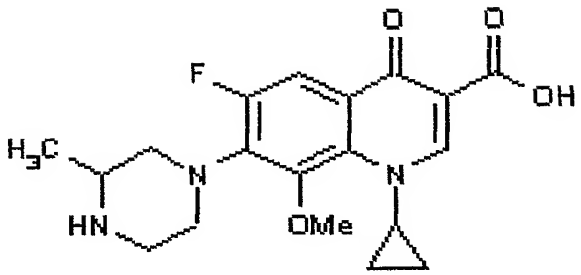
"PROCESS FOR OBTAINMENT OF STABLE INJECTABLE ISOTONIC SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, STABLE INJECTABLE SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, PROCESS OF PACKING THE OBTAINED INJECTABLE SOLUTION IN CLOSED SYSTEM, USE OF CLOSED SYSTEM FOR PACKING GATIFLOXACIN INJECTABLE SOLUTION, USE OF OBTAINED INJECTABLE SOLUTION OF GATIFLOXACIN-BASED PRE-DILUTED IN GLUCOSE, AND METHOD OF ADMINISTRATION".

Field of Invention

The present invention refers to injectable solution of gatifloxacin, pre-diluted in glucose, packed in flexible plastic bag made of tri-laminated film. The pre-diluted solution is presented ready for administration to the patient, being stored in closed system, thus preventing contamination risks. It also refers to the process of obtainment of the referred injectable solution, packing process, use of closed system for packing the injectable solution thus obtained and the method of administration.

Background of the Invention

Gatifloxacin is a synthetic antibacterial agent of wide spectrum for oral administration of the formula:



The chemical name is: (±)-1-cyclopropyl-6-fluoro-8-metoxy-7-(3-methyl-1-piperaziline)-4-oxo-3-quinolincarboxylic sesquihydrated acid.

The molecular formula is $C_{19}H_{22}FN_3O_4$ and the molecular weight is 402.42 and in the sesquihydrated form the molecular formula is $C_{19}H_{22}FN_3O_4.11/H_2O$. (The Merck Index – 13th Ed. – US, 2001).

This compound was developed by Kyorin, as described in its patents US 4980470 of 1987, US 5043450 of 27/08/1991 for the hemihydrated form, and US 5880283 of 09/03/1999 for the sesquihydrated form, which has advantages over the hemihydrated in pharmaceutical manufacturing. In this document is informed that in the hemihydrated form its weight values are increased with the increase of humidity in the ambient, and was informed that in tablet form containing hemihydrate, the disintegration and dissolution rates are low, which brings disadvantages in the pharmaceutical manufacturing. It is also indicated that in hydrochloryde form, the instability of the product due to its hygroscopic capacity is inconvenient, besides the evident problems of its low dissolution and disintegration when the product is transformed into

tablets. The sesquihydrated form of gatifloxacin described in this citation would overcome such inconveniencies. However, a ready for use stable suspension is not suggested in this document, which primarily aims at obtainment of the product stability in solid form for oral administration and quick disintegration under different humidity conditions.

Also aiming at preparation of the medicament for oral administration in the form of tablets, the pentahydrated form of gatifloxacin is described in document US 6413969 of 02/07/02, presented in oral solid form or powder for water suspension in oral administration.

It is also taught in this document that hemihydrate and sesquihydrate forms showed a defined tendency to form higher hydrates in the presence of water. Thus, it constitutes an objective of this invention to provide a pentahydrate of gatifloxacin under very high homogeneous condition, pharmaceutically more advantageous than the forms previously known, and that may be used to prepare stable pharmaceutical dosages, including an aqueous suspension, showing itself as a form physically stable which, throughout the time, has no tendency to convert into another crystalline form.

Another patent document, US 6333045 of 25/12/01, also presents the obtainment of a stable gatifloxacin as an objective, in which the problems

with color and precipitation of gatifloxacin crystals would be resolved by the addition of disodium edetate in aqueous medium containing gatifloxacin and salts thereof, for ophthalmic and otorhinological use.

Similarly, such anteriority does not anticipate a formulation in the solution of the present invention and the possibility of use in previous gatifloxacin forms, mainly the sesquihydrated form, evidently efficient for a great volume of gram-positive and gram-negative bacterial, applicable in a wide range of therapeutic uses, and particularly, does not suggest its use in packing of tri-laminated bag of closed system, which is of particular interest for the indications of gatifloxacin use in high doses and/or in hospital ambient, highly susceptible to contamination through improper handling, among other risk conditions.

Gatifloxacin is a crystalline powder, from white to slightly yellow color. It is presented as a racemate, with no optical rotation. The solubility of gatifloxacin depends on the pH, being that the maximum aqueous solubility thereof (40-60 mg/ml) occurs with pH between 2 and 5.

Gatifloxacin is a 8-metoxy fluoroquinolone with *in vitro* activity against wide spectrum of aerobic and anaerobic microorganisms, gram-positive and gram-negative. Gatifloxacin is also active against atypical microorganisms clinically

important. Gatifloxacin has a 8-methoxy group that showed to increase the bacterial action, reduce the development rate of resistance to quinolones and increase the inhibition of girase-DNA. Gatifloxacin antibacterial action results from the inhibition of girase-DNA and from topoisomerase IV. Girase-DNA is an essential enzyme, involved in replication, transcription and reparation of DNA-bacterial. Topoisomerase IV is an enzyme known for developing a key-function in the division of chromosomal DNA during the bacterial cellular division.

Contrary to several quinolones, the antibacterial activity of gatifloxacin is not affected by the inhibitors of proteic synthesis or of RNA and does not require cellular division. The action mechanism of fluoroquinolones, including gatifloxacin, is different from the mechanism of penicillin, cephalosporin, aminoglucosides, macrolide and tetracycline. Thus, fluoroquinolones may be active against pathogen that are resistant to other antibiotics.

There is no crossed resistance between gatifloxacin and the antibiotic classes previously mentioned. Based on *in vitro* synergism tests, gatifloxacin showed, in general, to be an additive to antibiotics of other classes in relation to bacterial inhibition. (Manual of Anti-microbial Prophylaxis and Therapy - Maria Beatriz Souza Dias, et al - 2001).

Gatifloxacin showed to be active, *in vitro*

and in clinical infections, against the majority of microorganism strains, either *in vitro* or in clinical infections such as: *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus pneumonie, Streptococcus β-hemolytic, Acinetobacter Iwoffi, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebisiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, Neisseria gonorhroeae, Chlamydia pneumoniae, Legionella pneumophila and Mycoplasma pneumoniae.*

For carrying out the sensibility tests, quantitative methods are used for determining the minimum inhibitor of anti-microbial concentrations (MIAMCs). These MIAMCs give estimates in relation to the sensibility of the bacteria in relation to anti-microbial compounds. The MIAMCs should be determined with the use of a standardized procedure. The standardization of the procedures is based on dilution methods (bouillon or agar) or equivalent (e.g. E-test) with standardized concentrations of inoculums and standardized concentrations of gatifloxacin. MIAMCs values are knowingly interpreted in accordance with the criteria established in Table 1.

The quantitative methods requiring the measurement of the diameter zone, also provides reproducible estimates of the sensibility of the

bacteria for the antimicrobial compounds. One of these standardized procedures needs the use of standardized concentrations of inoculums. This procedure uses discs impregnated with 5 µg of gatifloxacin for the sensibility tests of microorganisms to gatifloxacin. The reports obtained from the laboratorial results of the standard sensibility test on disc with 5 µg of gatifloxacin should be interpreted according to the criteria established in Table 2.

Generally, gatifloxacin is administered in racemate form, with disposition and antibacterial activity of the enantiomers R- and S-, virtually identical. Gatifloxacin was chemically planned for maximizing its antibacterial activity and reduce the probability of antimicrobial resistance by the addition of a cyclopropyl group in N-1 position and a methoxy group in C-8 position, minimize its toxicity by the absence of the halide in C-8 position, which provides a great reduction of the phototoxicity potential, and the addition of the piperazinyl group in C-7 position that minimizes the link to GABA receptor and reduces the risk of dizziness and optimize its pharmacokinetic by the addition of a methyl group in substitution to the piperazinyl group in C-7 position, which extends the half-life (maintaining the daily single dose), provides metabolic stability (evidenced by the elimination of unaltered drug, mainly by renal via), and may minimize the interaction with the

enzymes that metabolizes the drug, with the corresponding reduction of the drug-drug interaction risks based on the metabolism.

Gatifloxacin is well absorbed in the gastrointestinal tract after oral administration and may be ingested without taking the meals into consideration. The absolute bioavailability of Gatifloxacin is of 96%. Gatifloxacin plasmatic concentration peaks occur between 1 and 2 hours after the oral administration.

Gatifloxacin oral and intravenous administration routes may be considered as interchangeable, since gatifloxacin pharmacokinetic after the intravenous administration is similar to that observed after oral administration, when both are administered in equal doses.

The average pharmacokinetic parameters of gatifloxacin after intravenous infusions of 200 mg and 400 mg of single or multiple forms within periods of 1 hour are listed in Table 3.

Gatifloxacin pharmacokinetic is linear and time-independent when administered in doses ranging from 200 to 800 mg for a period of up to 14 days. The concentrations in the equilibrium state are achieved on the third day of gatifloxacin dose. In equilibrium state, the maximum and minimum plasmatic concentrations, achieved after a dose regime of 400 mg, once a day, are approximately 4,6 µg/ml and 0,40 µg/ml for the intravenous dose.

Gatifloxacin linkage to the plasmatic

proteins is approximately 20%, concentration-independent. The average volume of gatifloxacin distribution in equilibrium state (Vd_{ss}) ranged from 1.5 to 2.0 l/kg. Gatifloxacin is widely distributed in the organism in several tissues and body secreta, as shown in Table 4. The quick distribution of gatifloxacin in the tissues, results in higher concentrations of gatifloxacin in the majority of the target tissues than in the serum.

Gatifloxacin suffers a limited bioalteration in humans, with less than 1% of the dose eliminated in the urine, in the form of the ethylenediamine and methylenediamine metabolites.

Studies *in vitro* with isoenzymes of the cytochrome P450 (CYP) indicate that gatifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2, suggesting that gatifloxacin probably does not change the pharmacokinetic of the drugs metabolized by these enzymes (e.g., theophylline, cyclosporin, warfarin, midazolam).

Studies *in vivo* carried out in animals and in men indicate that gatifloxacin is not an enzymatic inductor. Therefore, it is unlikely to change its own metabolism or of other drugs that are concurrently being administered.

With reference to the elimination, more than 70% of a dose of gatifloxacin of the present invention was recovered in unaltered form in the urine, 48 hours after oral and intravenous

administration, and 5% was recovered in feces. Less than 1% of the dose was recovered in the urine, in the form of two metabolites. Gatifloxacin crystals were not observed in patients having received doses over 800 mg.

Gatifloxacin is eliminated as unaltered drug, mainly by renal via. The half-life of gatifloxacin average elimination is of 7 to 14 hours, irrespective of the dose and administration via. The renal clearance is dose-independent and its average values range from 124 to 161 ml/minute. The extent of this value, together with the significant reduction in gatifloxacin elimination observed upon the concurrent administration of probenecid indicates that gatifloxacin is subjected to glomerular filtration and tubular secretion. Gatifloxacin may also be subjected to biliary and/or intestinal elimination, since 5% of the dose was recovered in the feces as unaltered drug.

Gatifloxacin pharmacokinetics was similar in healthy volunteers and in patients with infection upon considering the renal function. Gatifloxacin pharmacokinetics in patients under 16 years of age was not established.

The dosage adjustment is not necessary due to the patient's ethnic. The individuals' ethnic did not significantly affect Gatifloxacin pharmacokinetic.

The dosage adjustment is not necessary in patients with liver failure. On account of the

quinolones antimicrobial activity being concentration-dependent, it is not expected that C_{max} values, slightly higher in patients with hepatic impairment, to cause negative impact on the result of the treatment in this kind of patients population.

In patients with renal impairment there is a reduction in gatifloxacin clearance and an increase in systemic exposure. It is recommended to reduce the dosage in patients with creatinine clearance < 30 ml/minute.

With reference to glucemic homeostasis, no clinically significant alterations were observed in glucose tolerance (by evaluation of the oral glucose tolerance curve) and the glucemic homeostasis (by evaluation of the fasting serum glucose, serum insulin and C-peptide), after single or multiple doses by intravenous infusion of 200 mg to 800 mg of Gatifloxacin of present invention, in healthy volunteers, in patients with type 2 diabetes (non-insulin-dependent mellitus diabetes).

Also, no electrocardiograph alterations were observed (remarkably in relation to QTc interval) after single or multiple intravenous doses (200, 400, 600 and 800 mg by one hour intravenous infusion) in healthy volunteers and in patients with type 2 diabetes.

No clinically significant alterations were observed in spirometry after single or multiple doses of 200, 400, 600, and 800 mg by intravenous

infusion in healthy individuals.

As previously emphasized, for Gatifloxacin traditional forms, problems in drug stability were identified, of which the solution was being pursued until the present invention.

Another problem common to the use of drugs administered to patients needing to undergo an anti-bacterial treatment, refers to security in the administration of such medicaments in interned patients, to which the oral administration of high potency drugs showed to be inadequate or improper considering the patient's conditions, with endovenous administration being indicated in such cases. Also, other forms for administering medicaments were indicated as involving high risk factors in view of the insecurity that could be involved in the administration thereof.

A study carried out in American hospitals showed that the most common medicament errors made in the infirmaries researched were: time error, omission, wrong dosage and administration of non-authorized drug. Generally, in 19% of the doses occur errors, being that 17% of the errors occur in the administration of wrong doses.

Incorrect doses in administering medicaments may result in calculation errors or error in preparing the dose, incorrect administration of the dose sequence, incorrect administration of the dose oriented by the pharmacy, incorrect change of the medicament in the

patient's medicament compartment and borrowing the dose to another patient.

Aiming at minimizing the opportunity of errors in the administration of medicaments in the hospital, some basic procedures should be observed, such as: check the dose based on the medical prescription, use the single dose system, which provides immediate administration of the medicament, and reduce the preparation of the medicament by intravenous media (IV) in the infirmaries, preferably using prepared medicaments (ready for use) that do not need previous dilution in the hospital.

Some hospitals in the United States have a type of certificate called Accreditation that would be a total quality program in the hospitals that certify the several processes adopted in the hospital. In Brazil, Accreditation is just beginning to be implemented in some hospitals.

The errors observed in this study were found in hospitals with strong quality control process.

In Brazil it is believed that the errors may be even greater since there is no control in hospital's process.

The use of pre-diluted medicaments packed in plastic bags reduces the risk of errors in preparation of medicaments besides reducing the risks of contamination in hospitals.

Although the Brazilian Patent PI 1100195

refers to derivatives of quinolonecarboxylic acid used as anti-bacterial agents and process for preparation thereof, this document does not describe the proper form of pharmaceutical presentation, but only mention that may be used in forms pharmaceutically well known when administered to humans or animals, however, without claiming, mentioning or suggesting that such active principle is pre-diluted and afterwards, packed in closed system similar to the one proposed by the present invention. More precisely, the citation does not also refer to Gatifloxacin in sesquihydrated form under the conditions proposed in the present application.

The presentation of a safe, sterile and stable solution for Gatifloxacin administration, as proposed in the present application, was not suggested by the state of art, by citations or other document prior to the present invention.

Similarly, neither the process for obtainment of the product previously diluted, nor the packing process of the referred to product are suggested, not even the administration process thereof.

Packing Usually Used:

Glass Ampoules and Flasks

The majority of the medicaments destined to administration by parenteral via, are packed in glass ampoules or flasks. Glass is widely used for

being an inert material, not occurring change of components with the stored solution.

However, these medicaments must be pre-diluted, generally in isotonic solutions (sodium chloride or glucose), in order to reduce the aggression upon the administration to patient.

Plastic Materials

The use of plastic in packing pharmaceutical products is advantageous, either for resistance to breaking, therefore, giving security to professionals and patients, or by the manufacturing facility of such containers.

The plastic materials most used in the constitution of containers for pharmaceutical products are: polyethylene, polypropylene, polyvinyl chloride (PVC) and ethylene vinyl acetate (EVA). However, these materials are not totally inert and may interact with the medicaments and originate processes related with permeability, removal, absorption and/or adsorption and chemical reactions.

Parenteral solutions require more care in relation to definition of the packing material to be used.

PVC Flexible Plastic Bag

The flexible plastic bag made of polyvinyl chloride (PVC) has compatibility with several medicaments. Polyvinyl chloride constitutes an excellent barrier for humidity and for gases, in

general, but plasticizing materials reduce such properties. Also presents transparency, which allows the visualization of the solution. Moreover, it has a way for addition of medicaments.

Several medicaments in many medical specialties use as solvent, parenteral solutions of great volume and many of these medicaments may not be administered in bags or even in equipment made of PVC, due to several reasons. The main one is PVC incompatibility with medicaments, as for example, Paclitaxel. Other medicaments adhere to the walls of PVC bag, and when administered, the patient receives a quantity lower than the necessary. Others also reduce its potency, possible to achieve only 45% of the total.

Some medicaments are incompatible with PVC such as: *Cyclosporine*, an immunosupressant that is used in the treatment of patients with transplanted organs such as kidneys, pancreas, liver and heart. *Paclitaxel*, antineoplastic, indicated for treatment of ovarian metastatic carcinoma and breast cancer. *Carnustine*: antineoplastic, indicated for the palliative therapy in cerebral tumors, multiple myelomas, lymphomas and other tumors. *Teniposido*: antineoplastic, indicated for the treatment of malign lymphomas, Hodgkin decease, lymphoblastic leukemia, intracranial tumors, bladder carcinoma and other tumors. Nitroglycerin: coronary vasodilator, indicated for the treatment of pre-operative hypertension for controlling congestive

cardiac impairment, in adjustment of acute myocardial infarct. *Nimodipine*: calcium antagonist that is a calcium antagonist agent, selective with vasodilator action on cerebral arteries. *Diazepam*: anxiolytic, indicated for basal sedation prior to therapeutic procedures or interventions as cardiac catheterism, radiological exams, biopsies among others. *Propofol*: sedative; Propofol is an intravenous general anesthetic agent of short action, proper for induction and maintenance of general anesthetic in chirurgical procedures of adult and children over 3 years of age.

The contact between PVC materials and the concentrate used in solutions preparation is not advisable. For minimizing the patient exposure to plasticizers, which may be released from PVC bags, the medicaments should be stored in glass flasks or in polypropylene or polyolephine bags. The equipment should be made of polyethylene and not PVC.

With reference to the antineoplastic Camustine, the studies carried out showed that the use of the same in plasticizing containers made of polyvinyl chloride (PVC) is non-advisable since carnustine suffers adsorption when used in PVC bags. With reference to antineoplastic Teniposido, in order to prevent the extraction of the plasticizer DEPH from container made of polyvinyl chloride (PVC), the solutions should be prepared and administered through great volume containers

and devices not containing DEHP. With reference to the coronary vasodilator Nitroglycerine, it was observed that nitroglycerine promptly migrates in many plastics, including in PVC. The absorption of nitroglycerine through PVC tubes is much higher when the tube is long. In studies published using PVC, it was verified that the fraction that migrates from the original content of nitroglycerine was of 20 to 60%. For the calcium antagonist Nimodipine, as the active substance is absorbed by PVC, the use of polyethylene bags or glass is recommended. The equipment may not be made of PVC. Nimodipine is photo-sensible. For the anxyolitic Diazepam, special care should be observed since the tests carried out with diazepam in PVC bags have concluded that the concentration thereof was quickly reduced, decreasing to 15% in the first hour and 55% within 24 hours, that is, after administration of diazepam in PVC bags at the end of the test, it was verified that after 24 hours the concentration was only 45% of the start and, for the sedative Propofol that is diluted in 5% glucose solution, the product literature does not discriminate the use of PVC bags, but many reference centers do not use PVC bags fearing the migration, or even due to release of the plasticizer polyvinyl chloride.

Closed System

The concept of closed system in parenteral

solutions is based on the fact of existing no contact of the ambient with the solution to be administered, thus preventing microbial contamination through the air or contact during coupling of the administration equipment.

Parenteral solutions may be packed in plastic flasks being then designated as open system, where no total protection against contamination exists. In this case, there is vacuum formation during the product administration to the patient, reducing the dropping speed. Moreover, medicaments are added to the flask through the removal of the equipment coupled to the flask, existing higher risks of contamination.

The plastic bag (PVC or Tri-laminated) constitutes a closed system because does not allow the contact of the ambient with the solution to be administered. It is a flexible recipient that needs no air inlet for administration of the solution. It is emptied by lability through atmospheric pressure action, eliminating the risks of contamination by air or contact, either of the air with the solution, or of micro-particles that may have access to the solution through needle perforation.

The bags manufactured with tri-laminated presents more security since the PVC bags may, in contact with medicaments, increases DEHP lixiviation and studies carried out indicate that DEHP has potential to produce side effects in human reproductive system.

Starting from this principle, the present invention is proposing to pack Gatifloxacin injectable solution pre-diluted in glucose, in this closed system, thus preventing the inconveniences found in the state of art.

Invention

The present invention concludes that the use of pre-diluted preparations in closed system reduces the risks of errors in the administration of medicaments, reducing the handling phases of the medicament by the nursing staff of the hospital, further to reducing the contamination risks.

The product obtained by the present invention is presented in the form of Gatifloxacin injectable solution pre-diluted in glucose, packed in tri-laminated flexible plastic bag (closed system).

Through the glucose pre-diluted formulation and the closed system, the contamination risks through air or contact during the administration is prevented. An isotonic solution of 5% glucose is added to the formulation, where diluted Gatifloxacin is maintained stable if packed in tri-laminated flexible plastic bag.

Through the present invention the referred to solution is prepared, pouring 1,600 l of water for injection into a stainless steel tank, followed by the addition of hydrochloric acid up to pH 2.0 to 5.0. The ideal range for the water solution with

hydrochloric acid is pH 2.5 to 4.5. Then, anhydrous glucose is added under stirring during 8 to 12 minutes, being the preferred stirring rate of 10 minutes, with possible dropwise addition of hydrochloric acid in event the solubilization does not occur within appropriate time. A solution of sodium hydroxide is slowly added to the process, which was previously solubilized in 500 ml of water for injection. Sodium hydroxide is added until the pH of the solution is stabilized from 3.5 to 5.5, preferably from 4.0 to 5.0. Finally, the volume is completed to 2,500 l stirring afterwards during a period from 12 to 18 minutes, being preferable that the stirring occurs for about 15 minutes.

Gatifloxacin is more soluble in pH from 2.0 to 5.0. The solutions most commonly used for dilution are glucose and sodium chloride in isotonic concentrations. Glucose has pH from 3.5 to 5.5, being the ideal range from 4.0 to 5.0. Whereas, sodium chloride has pH from 4.5 to 7.5, being the ideal range from 5.0 to 7.0. Then, we have opted for the pre-dilution in 5% glucose since it refers with a solution where Gatifloxacin stability is maintained at a pH range more compatible with the stability thereof.

Gatifloxacin solution pre-diluted in 5% glucose (end product) should present a content of Gatifloxacin from 90 to 110%, being the ideal range from 97 to 103%. The glucose content in the solution should stay between 95 to 105%, being the

ideal range from 98 to 102%.

After conclusion of the preparation, the solution will be analyzed, and afterwards packed in tri-laminated plastic bag.

Through the process of the present invention, the solution obtained presents the following characteristics for each ml:

Gatifloxacin ---------- 2 mg
Anhydrous glucose ---------- 50 g
Hydrochloric acid ---------- 0.0004062 ml
Sodium hydroxide q.s. ---------- pH 3.5 to 5.5
Water for injectables q.s. ---------- 1 ml

The solution is diluted in 5% glucose, in order to obtain an isosmotic and isotonic solution in relation to blood cells, that is, should present osmolarity equal to 300m osmolar. During the studies on stability it was possible to observe that the Gatifloxacin solution in 5% glucose was maintained stable throughout the study period, and no physical and chemical alteration of the packing material occurred by the medicament and vice-versa. No degradation product was detected during the studies (Table 5A, B, C, D, F - study on the stability of Gatifloxacin in glucose, packed in plastic bag.

The present invention also refers to Gatifloxacin-based injection solution, pre-diluted in glucose packing process in closed system, using tri-laminated flexible plastic bag for performing the packing.

The plastic bag is made of a film composed of three distinct layers, each having a particular protection function. The film is produced through a co-extrusion process where the layers are grouped forming a single blade. This process is ideal for packages wherein each external layer should not obligatorily interact with the product.

The layers are: polyester (external layer), polyethylene (intermediary layer) and propylene copolymer (internal layer). Polyester is a heat-resistant material, is transparent and has excellent resistance to mechanical and abrasive stresses. Polyethylene provides excellent flexibility and due to its properties acts as a barrier in humidity and vapor exchange between the ambient. Propylene copolymer is waterproof and presents excellent flexibility; the main characteristic of which is chemically inert.

Advantages of Tri-laminated Plastic Bag

The parenteral solutions packed in tri-laminated show the characteristics adequate for the security concept established for the closed system. The compatibility of the bag with any type of medicament is among them. The advantages of its packing go further, outstanding its excellent collapsing action, non-existence of plasticizers that may migrate to the solution and non-aggression to the environment, even in event of incineration.

Tri-laminated offers advantages not yet

achieved with other plastics used in plastic bags. For not containing any type of plasticizer, as DEPH, knowingly carcinogenic, there is no risk of contamination of the solution.

Some plastics, as PVC, may release substances to the solutions or dilute substances in the solutions that are in contact with plastic.

The plastic bag made of tri-laminated film, has the following advantages in relation to other packing types:

- Transparency: allows a careful visual inspection prior to use.
- Flexibility: complete collapsing allows total administration of its content with no need of air inlet.
- Thermal resistance: allows sterilization at 121° C (depending on the stored medicament).
- Absence of plasticizer: there is no contamination of the solution by migration of the plasticizer, showing low level of extractable substances.
- Mechanical resistance: assures security in transportation, with no risk of showing micro-holes or cracks.
- Highly waterproof (impermeable).
- Excellent chemical inertia: (compatibility with several medicaments, since the internal layer is constituted of propylene copolymer).
- Low discarding volume.
- Easy incineration, non-aggressive to the environment.

Biocompatibility

Complying with USP class VI specifications and JP XIII (Japanese pharmacokinetics):

- Systemic toxicity: non-significant systemic reaction.
- Intra-cutaneous toxicity: non-significant tissue reaction.
- Implementation test: non-significant reaction.
- Hemolysis test *in vitro*: average value 0%.
- Pyrogen test *in vitro*: negative.
- Cytotoxity test: absence of reactivity.

The packing process of the injection solution of Gatifloxacin-based pre-diluted in glucose, in a closed system of tri-laminated flexible plastic bag type, follows the operation hereunder: the bags are fitted in the filling needle of the filling machine, the pedal is pressed until complete filling of the bag. The same is removed from the machine and the connector is fit in the bag nozzle using cyclohexanone for closure. The closed bag is then transported through the conveyor and inserted in the aluminum external packing, which is then welded. The bags are packed on trays and fit on the transporting car and then taken to the autoclave platforms in order to be autoclaved in counter-pressure autoclave.

The invention also refers to the use of tri-laminated flexible plastic bag of closed system type for packing the Gatifloxacin-based injectable solution, pre-diluted in glucose obtained in

accordance with the present invention.

The tri-laminated flexible bags were manufactured in PLUMAT Equipment, which presents an uncoiling and film feeder device, an uncoiling and tube feeder device, a press for stamping on the tube Hot Stamp, a press for heat welding the body (bag), a press for heat welding the tube, trimmer and outlet conveyor. Upon starting the process, the laminated is uncoiled, the bag stamping occurs, and the same carries on to the matrix where the heat welding of the structure thereof occurs. The tubes are directed to the feeder up to the electrodes, suffer a preheating and afterwards are welded onto the bags. The edges are trimmed off and the bag is removed from the internal conveyor and transferred to the external conveyor, thus the product shown in Figure 1 is obtained.

Finally, the invention refers to the method for administering to patients the injectable solution of Gatifloxacin-based, pre-diluted in glucose and packed in tri-laminated flexible plastic bag of closed system type, eliminating completely the contact of the ambient with the solution to be administered, thus preventing microbial contamination through air or contact during the connection of the administering equipment.

The injectable solution Gatifloxacin-based, pre-diluted in glucose, packed in closed system of tri-laminated flexible plastic bag type shows

antimicrobial action of wide spectrum and the following indication may be mentioned: community acquired pneumonia, bacterial acute exacerbation of chronic bronchitis, acute sinusitis, non-complicated infections of skin and cutaneous structures, non-complicated infections of urinary tract (cystitis), complicated infections of urinary tract, pyelonephritis, non-complicated urethral, pharyngeal and rectal gonorrhea, in patients of the male sex; endocervical, pharyngeal and rectal gonorrhea, in patients of the female sex, among others.

Example I

Study on stability - Gatifloxacin in glucose 2 mg/ml

Objective

Establish the adequate packing conditions, packing specifications, and establishment of the validity term and the correct practices of Quality Control.

Samples were collected, which were stored at room temperature (30°C ± 2°C) and analysis carried out during the established period: 3 months, 6 months, 9 months, 12 months and 24 months after starting the analysis. Samples of the bags containing 2mg/ml Gatifloxacin in glucose, laboratory glasses, specific reagents for dosage, material for sterilization, pyrogen and apparatus of high power liquid chromatography, were used.

Test procedure

The batch used was sterilized at 107°C and 58 bags were collected, out of which 34 were stored in the Stability Room for carrying out the natural stability study and 22 were used for the initial analysis. The daily humidity and temperature control (70% ± 5% RH / 30°C ± 2°C) was carried out inside the room.

The analytic method used for analyzing Gatifloxacin (active principle) was made by high power liquid Chromatography (HPLC). The products packed in the bags should remain with its original characteristics, according to purity, quality and efficiency specifications thereof.

Characteristics of the Product

a) Physical Characteristics:

The following physical properties should be preserved: aspect, purity, absence of unknown particles and airtightness.

b) Chemical Characteristics:

The degradation of the active principles should not be higher than 5% and should not have unknown substances in the product composition.

c) Biological Characteristics:

The bag should remain sterile, apyrogenic and atoxic.

According to the study carried out, it was possible to observe that no physical or chemical incompatibility of the packing with Gatifloxacin

solution in 5% glucose occurred, maintaining its stability until the end of the proposed period (24 months).

TABLE 1: CRITERIA ESTABLISHED FOR INTERPRETING MIAMC VALUES.

For non-fastidious aerobe organisms:

MIAMC (µg/ml)	Interpretation
2.0	Sensible (S)
4.0	Intermediary (I)
8.0	Resistant (R)

For *Haemophilus* spp [a]:

MIAMC (µg/ml)	Interpretation
2.0	Sensible (S)

[a] This interpretation standard is applicable only to micro-dilution sensibility tests with *Hemophilus* spp, using *Haemophilus* (HTM) medium test.

For *Streptococcus* spp. Including *Streptococcus pneumoniae* [b]

MIAMC (µg/ml)	Interpretation
1.0	Sensible (S)
2.0	Intermediary (I)
4.0	Resistant (R)

[b] These interpretation standards are applicable only to micro-dilution sensibility tests using adjusted cation bouillon and Mueller-Hilton with equine blood lysate.

For *Neisseria gonorrhoeae* [c].

MIAMC (µg/ml)	Interpretation
0.125	Sensible (S)
0.25	Intermediary (I)
0.5	Resistant (R)

[c] These interpretation standards are applicable to Agar tests with CG Agar and growing supplement defined at 1%.

For anaerobic bacteria:

MIAMC (μg/ml)	Interpretation
2.0	Sensible (S)
4.0	Intermediary (I)
8.0	Resistant (R)

TABLE 2: CRITERIA ESTABLISHED FOR INTERPRETING THE REPORTS OBTAINED FROM LABORATORIAL RESULTS OF THE STANDARD SENSIBILITY TEST ON DISC WITH 5 μG GATIFLOXACIN.

For non-fastidious aerobic organisms:

Zone Diameter (mm)	Interpretation
18	Sensible (S)
15-17	Intermediary (I)
14	Resistant (R)

For *Haemophilus* spp [g]:

Zone Diameter (mm)	Interpretation
18	Sensible (S)

[g] This standard of zone diameter is applicable only to tests with *Haemophilus* spp using *Haemophilus* test medium (HTM).

For *Streptococcus* spp, including *Streptococcus pneumoniae* [h]

Zone Diameter (mm)	Interpretation
18	Sensible (S)
15-17	Intermediary (I)
14	Resistant (R)

[h] These standards of zone diameter are applicable only to tests using Agar supplement of Mueller-Hilton in sheep blood at 5% incubated in CO_2 at 5%.

For *Neisseria gonorrhoeae* [i]

Zone Diameter (mm)	Interpretation
38	Sensible (S)
34-37	Intermediary (I)
33	Resistant (R)

[i] These interpretation standards are applicable to diffusion tests on discs with CG Agar and defined growth supplement at 1% in CO_2 at 5%. The interpretation involves the correlation of the diameter obtained in the disc test with Gatifloxacin MIAMC.

TABLE 3: LISTS GATIFLOXACIN AVERAGE PHARMACOKINETIC PARAMETERS AFTER INTRAVENOUS INFUSIONS OF 200 mg AND 400 mg IN SINGLE AND MULTIPLE FORM, IN HOUR PERIODS.

Gatifloxacin pharmacokinetics parameters (± Average Standard Deviation)

	C_{max} (µg/ml)	aT_{max} (hours)	AUC[b] (µg.h/ml)	$T_{1/2}$ (hours)	Vd_{ss} (1/kg)	Cl (ml/min)	Cl_R (ml/min	RU (%)
GATIFLOXACIN IV 200 mg								
Single dose (n=12)	2.18 ± 0.26	1.00 (0.67, 1.50)	15.9 ±2.6	11.08 ± 4.06	1.9 ± 0.1	214.4 ± 36.5	154.9 ± 32.0	71.7 ± 6.82
Multiple dose (n=8)[e]	2.38 ± 0.36	1.00 (0.67, 1.50)	16.8 ± 3.6	12.31 ± 4.55	2.0 ± 0.3	207.0 ± 44.0	154.7 ± 55.1	72.4 ± 16.4

GATIFLOXACIN IV 400 mg								
Single dose (n=30)	5.52 ± 0.99	1.00 (0.50, 1.00)	35.1 ± 6.7	7.43 ± 1.56	1.5 ± 0.2	196.1 ± 33.4	123.7 ± 40.9	62.3 ± 16.7
Multiple dose (n=5)	4.56 ± 0.61	1.00 (1.00, 1.00)	35.4 ± 4.6	13.90 ± 3.89	1.6 ± 0.5	190.5 ± 24.0	161.0 ± 42.6	83.5 ± 13.8

[a] Average (minimum; maximum)

[b] Single dose: AUC(0-); multiple dose: AUC (0-24)

[c] n=184 for Cl; n=134 for Cl_R and n=132 for RU

[d] Based on the pharmacokinetic model of patients population; n=103 for C_{max} and n=7 for Cl_R and RU

C_{max}: Maximum serum concentration

T_{max}: Time for achieving maximum serum concentration (C_{max})

AUC: Area under the concentration curve by the time

$T_{1/2}$: Serum half-life

Vd_{ss}: Volume of distribution in balance state

Cl: Total clearance IV and total oral apparent clearance

Cl_R: Renal clearance

RU: Urinary recovery

TABLE 4: GATIFLOXACIN DISTRIBUTION IN THE ORGANISM IN SEVERAL TISSUE CORPOREAL SECRETA.

Tissue or Secretion	Ratio tissue-fluid/serum (range)*
Respiratory	
Alveolar macrophages	26.5 (10.9-61.1)
Bronchial mucous	1.65 (1.12-2.22)
Secretion of pulmonary epithelial wall	1.67 (0.81-4.46)
Pulmonary parenchyma	4.09 (0.50-9.22)
Sinusoidal mucous	1.78 (1.17-2.49)
Mucus (multiple dose)	1.28 (0.49-2.38)
Middle ear mucous	4.10 (0.34-4.55)
Musculoskeletal, skin	
Secretion of cutaneous blisters	1.00 (0.50-1.47)

Bones	0.62 (0.16-1.95)
Gastrointestinal	
Saliva	0.88 (0.46-1.57)
Bile	5.34 (0.33-14.0)
Central Nervous System	
Cerebrospinal (multiple dose)	0.36 (0.21-0.45)
Reproductive Organs	
Prostate	1.88 (1.11-3.28)
Prostatic Secretion	1.23 (1.05-1.72)
Ejaculated	1.07 (0.86-1.32)
Seminal liquid	1.01 (0.81-1.21)
Vagina	1.22 (0.57-1.63)
Uterine collum	1.45 (0.56-2.64)
Endometrium	1.95 (0.77-2.83)
Myometrium	1.63 (0.57-2.20)
Fallopian Tube	1.49 (0.53-2.56)
Ovarian	1.80 (0.69-3.07)

*Average values of 24 hours after administration of single doses (100, 150, 200, 300 and 400 mg) and multiple (150 and 200 mg, twice a day) of GATIFLOXACIN, according to the present invention, except for secretion of cutaneous blisters and saliva, which value presented refers to average AUC.

TABLE 5 (A, B, C. D, F): STABILITY STUDY ON GATIFLOXACIN IN GLUCOSE - 2mg/ml (GATIFLOXACIN) PACKED IN PLASTIC BAG - 200ml - TRI-LAMINATED (LONG TERM STABILITY - 30°C ± 2°C)

TABLE 5 A:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN IV)
Batch Number: S023 Manufacture Date: 08/02/2000
Packing Material: Plastic Bag - 200ml - Tri-laminated
Results:

Long Term Stability - 30°C ± 2°C

Tests	Date	22/02/00	22/05/00	22/08/00	22/11/00	22/02/01	22/02/02
	Specification	Start	3 months	6 months	9 months	12 months	24 months
Description/ Color	Clear Liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90% to 110%	100.0%	99.8%	99.6%	99.5%	99.0%	98.89%
pH	**3.5 to 5.5**	5.0	4.9	4.76	4.5	4.36	4.0
Content: Glucose	95% to 105%	99.8%	99.5%	99.0%	98.7%	98.5%	98.0%
Sterility	Sterile	Sterile	-	-	-	-	According
Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	**Q.S. 58 bags**	2 bags	2 bags	2 bags	2 bags	2 bags	24 bags

TABLE 5 B:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN)

Batch Number: S024 Manufacture Date: 15/02/2000

Packing Material: Plastic Bag - 200ml - Tri-laminated

Results:

Long Term Stability - 30°C ± 2°C

Tests	Date	22/02/00	22/05/00	22/08/00	22/11/00	22/02/01	22/02/02
	Specification	Start	3 months	6 months	9 months	12 months	24 months
Description/ Color	Clear liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90% to110%	99.7%	99.5%	99.0%	98.78%	98.6%	98.0%
pH	3.3 to 5.5	5.03	4.67	4.56	4.50	4.3	4.23
Content: Glucose	95% to 105%	100.0%	99.8%	99.5%	99.0%	98.78%	98.5%
Sterility	Sterile	Sterile	-	-	-	-	According

Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	Q.S. 58 bags	2 bags	2 bags	2 bags	2 bags	2 bags	2 bags

TABLE 5 C:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN)

Batch Number: S025 Manufacture Date: 17/02/2000

Packing Material: Plastic Bag - 200ml - Tri-laminated

Results:

Long Term Stability - 30°C ± 2°C

Tests	**Date**	**22/02/00**	**22/05/00**	**22/08/00**	**22/11/00**	**22/02/01**	**22/02/02**
	Specification	**Start**	**3 months**	**6 months**	**9 months**	**12 months**	**24 months**
Description/ Color	Clear liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90% to 110%	101.0%	100.0%	99.8%	99.5%	99.0%	98.7%
pH	3.3 a 5.5	4.8	4.65	4.56	4.5	4.36	4.20
Content: Glucose	95% to 105%	100.0%	99.89%	99.7%	99.6%	99.5%	99.0%
Sterility	Sterile	Sterile	-	-	-	-	According
Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	Q.S. 58 bags	2 bags	2 bags	2 bags	2 bags	2 bags	2 bags

TABLE 5 D:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN)

Batch Number: S027 Manufacture Date: 18/02/2000

Packing Material: Plastic Bag - 100ml - Tri-laminated

Results:

Long Term Stability - 30°C ± 2°C

Tests	Date	22/02/00	22/05/00	22/08/00	22/11/00	22/02/01	22/02/02
	Specification	Start	3 months	6 months	9 months	12 months	24 months
Description/ Color	Clear liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90% to 110%	100.0%	99.7%	99.56%	99.4%	99.0%	98.7%
pH	3.3 to 5.5	4.6	4.36	4.26	4.18	4.12	4.0
Content: Glucose	95% to 105%	100.0%	99.4%	99.35%	99.0%	98.87%	98.5%
Sterility	Sterile	Sterile	-	-	-	-	According
Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	Q.S. 58 bags	2 bags	2 bags	2 bags	2 bags	2 bags	2 bags

TABLE 5 E:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN)

Batch Number: S028 Manufacture Date: 19/02/2000

Packing Material: Plastic Bag - 100ml - Tri-laminated

Results:

Long Term Stability – 30°C ± 2°C

Tests	Data	22/02/00	22/05/00	22/08/00	22/11/00	22/02/01	22/02/02
	Specification	Start	3 months	6 months	9 months	12 months	24 months
Description/ Color	Clear liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90% to 110%	99.8%	99.76%	99.6%	99.5%	99.0%	98.38%
pH	3.3 to 5.5	5.0	4.67	4.5	4.36	4.26	4.0
Content: Glucose	95% to 105%	101.0%	100.0%	99.97%	99.67%	99.5%	99.0%
Sterility	Sterile	Sterile	-	-	-	-	According
Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	Q.S. 58 bags	2 bags	2 bags	2 bags	2 bags	2 bags	2 bags

TABLE 5 F:

Product: Gatifloxacin in Glucose - 2mg/ml (GATIFLOXACIN)

Batch Number : S029 Manufacture Date: 21/02/2000

Packing Material: Plastic Bag - 100ml - Tri-laminated

Results:

Long Term Stability - 30°C ± 2°C

Tests	Date	22/02/00	22/05/00	22/08/00	22/11/00	22/02/01	22/02/02
	Specification	***Start***	***3 months***	***6 months***	***9 months***	**12 months**	**24 months**
Description/ Color	Clear liquid, slightly yellow	According	According	According	According	According	According
Content: Gatifloxacin	90%toa 110%	101.0%	100.8%	100.0%	99.86%	99.7%	99.5%
pH	3.3 to 5.5	4.76	4.56	4.5	4.37	4.29	4.16
Content : Glucose	95% to 105%	100.0%	99.5%	99.4%	99.0%	98.6%	98.5%
Sterility	Sterile	Sterile	-	-	-	-	According
Pyrogen	Apyrogenic	Apyrogenic	-	-	-	-	According
Analyzed samples	Q.S. 58 bags	2 bags	2 bags	2 bags	2 bags	2 bags	2 bags

Still under exampling title and not limiting, Figure 1 refers to presentation of tri-laminated flexible bag, as described in the present invention.

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CLAIMS

1. **PROCESS FOR OBTAINMENT OF STABLE INJECTABLE ISOTONIC SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, FOR USE IN CLOSED SYSTEM,** characterized by the following phases:

a) 1,600 l of water for injection was poured into a stainless steel tank, followed by the addition of hydrochloric acid up to pH 2.0 to 5.0.

b) Followed by the addition of anhydrous glucose, stirred during 8 to 12 minutes.

c) Followed by the addition of gatifloxacin until complete solubilization by stirring, during 8 and 10 minutes, with the possibility of adding hydrochloric acid in this phase, dropwise.

d) Slowly adding to the process a solution of sodium hydroxide, which was previously solubilized in 500 ml of water for injection.

e) Adding sodium hydroxide until the pH of the solution is stabilized from 3.5 to 5.5.

f) Fill the volume to 2,500 l, then stirring from 12 to 18 minutes.

2. **PROCESS** in accordance with claim 1, characterized by the fact that in phase (a) the ideal pH range for the water solution with hydrochloric acid is of 2.5 to 4.5.

3. **PROCESS** in accordance with claim 1, characterized by the fact that in phase (b) in

the addition of anhydrous glucose, the time for maintaining under stirring is preferably of 10 minutes.

4. **PROCESS** in accordance with claim 1, characterized by the fact that in phase (c) the time for maintaining under stirring is preferably of 10 minutes.

5. **PROCESS** in accordance with claims 1 and 4, characterized by the fact that in phase (c) hydrochloric acid may be added dropwise, in case the solubilization does not occur within the appropriate time.

6. **PROCESS** in accordance with claim 1, characterized by the fact that in phase (e) the pH of the solution is stabilized preferably from 4.0 to 5.0.

7. **PROCESS** in accordance with claim 1, characterized by the fact that in phase (f) the stirring preferably occurs during a period of 15 minutes.

8. **STABLE INJECTABLE SOLUTION OF GATIFLOXACIN PRE-DILUTED IN GLUCOSE, OBTAINED ACCORDING TO THE PROCESS DESCRIBED IN CLAIM 1,** characterized by the addition of 5% glucose, an isotonic solution, where the diluted gatifloxacin is maintained stable when packed in closed system.

9. **SOLUTION** in accordance with claim 8, characterized by the fact that the closed system being made of tri-laminated flexible plastic bag.

10. **SOLUTION** in accordance with claim 8 characterized by comprising a Gatifloxacin content from 90 to 110% and a Glucose content from 95 to 105%.

11. **SOLUTION** in accordance with claims 8 and 10 characterized by the fact of preferably containing 97 to 103% of Gatifloxacin.

12. **SOLUTION** in accordance with claim 10 characterized by the fact of preferably containing 98 to 102 % Glucose.

13. **SOLUTION** in accordance with claim 8 characterized for showing the following dosages for each ml: 2mg of Gatifloxacin, 50g of anhydrous Glucose, 0.0004062 ml of hydrochloric acid, sodium hydroxide q.s. pH from 3.5 to 5.5 and 1 ml of water for injection q.s.

14. **PROCESS OF PACKING GATIFLOXACIN SOLUTION IN CLOSED SYSTEM DESCRIBED IN CLAIM 8**, characterized by the fact of being processed in closed system, using tri-laminated flexible plastic bag for packing.

15. **PROCESS** in accordance with claim 14, characterized by the fact that the plastic bag is made of a film composed of three distinct layers.

16. **PROCESS** in accordance with claim 15, characterized by the fact that each film layer shows a particular protection function.

17. **PROCESS** in accordance with one of claims 15 or 16, characterized by the fact that the film is

produced through a co-extrusion process, where the layers are grouped forming a single sheet.

18. **PROCESS** in accordance with claim 17, characterized by the fact that the external layer is made of polyester, the intermediary layer is made of polyethylene and the internal layer is made of propylene copolymer.

19. **PROCESS** in accordance with claims 14, 16 or 18, characterized by the fact that, for the closed system, each material used has distinct functions, where polyester is heat resistance and has mechanical and abrasive stress resistance, polyethylene provides flexibility and acts as a barrier in the exchange of humidity and vapors between the ambient, and propylene copolymer is waterproof, flexible and inert.

20. **PROCESS** in accordance with claim 14, characterized by the packing being made through the following phases:

(a) Fit the bags in the filling needle of the packing machine and press the pedal until the filling of the bag is completed;

(b) Remove the bag from the machine and place the connector in the bag nipple using cyclohexanone for the closing;

(c) Transport the closed bag through the conveyer and place inside the aluminum external packing and weld, and

(d) Place the bag on a tray, fixed in the transporting trolley and direct it to the autoclave platform to be autoclaved in counter-pressure autoclave.

21. **USE OF CLOSED SYSTEM FOR PACKING GATIFLOXACIN INJECTABLE SOLUTION** characterized by the fact of serving for packing injectable solution, stable and isotonic, of gatifloxacin pre-diluted in 5% glucose.

22. **USE** in accordance with claim 21, characterized by the fact of such solution being packed in tri-laminated flexible plastic bag.

23. **USE** in accordance with claim 22, characterized by the fact that the material used in the packing plastic bag is composed of three distinct layers.

24. **USE** in accordance with claim 23, characterized by the fact that the external layer is made of polyester, the intermediary layer is made of polyethylene and the internal layer is made of propylene copolymer.

25. **USE** in accordance with claim 24, characterized by the fact that polyester is heat resistant and has mechanical and abrasive stress resistance, polyethylene provides flexibility and acts as a barrier in the exchange of humidity and vapors between the ambient, and propylene copolymer is waterproof, flexible and inert.

26. **USE** in accordance with claim 21, characterized for hindering the gatifloxacin solution from

being contaminated by the air or contact during the administration.

27. **USE OF INJECTABLE SOLUTION, GATIFLOXACIN-BASED, PRE-DILUTED IN GLUCOSE** characterized by the fact that the stable isotonic solution is pre-diluted in 5% glucose and packed in tri-laminated flexible plastic bag of closed system type and shows anti-microbial action of wide spectrum.

28. **USE** in accordance with claim 27, characterized by the fact of being used against community acquired pneumonia, bacterial acute exacerbation of chronic bronchitis, acute sinusitis, non-complicated infections of skin and cutaneous structures, non-complicated infections of urinary tract, cystitis, complicated infections of urinary tract; pyelonephritis; non-complicated urethral, pharyngeal and rectal gonorrhea, in patients of the male sex; endocervical, pharyngeal and rectal gonorrhea, in patients of the female sex.

29. **METHOD OF ADMINISTRATION OF GATIFLOXACIN-BASED INJECTABLE SOLUTION PRE-DILUTED IN GLUCOSE** characterized by the fact of administering to patients, by intravenous and parenteral via, the stable and isotonic injectable solution, gatifloxin-based pre-diluted in 5% glucose, packed in tri-laminated flexible plastic bag constituting a system of closed type.

30. **METHOD** in accordance with claim 29, characterized by the fact of eliminating the

contact of the ambient with the 5% gatifloxacin solution to be administered, preventing the microbial contamination through the air or contact during the connection of the administration equipment, thus reducing the risks of errors in the administration of drugs, as well as the reduction of the drug handling phases by the hospital nursing staff.

FIGURE 1